

L Number	Hits	Search Text	DB	Time stamp
-	2	("6156535").PN.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/14 15:53
-	24	(US-6156535-\$ or US-6159709-\$ or US-6171821-\$ or US-6300492-\$ or US-6331412-\$ or US-6133437-\$ or US-5919912-\$ or US-6495339-\$ or US-6472172-\$ or US-6228603-\$ or US-6107088-\$ or US-6087173-\$).did. or (US-20020137028-\$ or US-20020120121-\$ or US-20020086409-\$ or US-20020187946-\$ or US-20020160975-\$ or US-20020132786-\$).did. or (WO-9835693-\$ or WO-9726331-\$ or WO-9706255-\$ or WO-9612016-\$).did. or (JP-11032780-\$).did. or (US-5919912-\$).did.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/14 16:09
-	372	BIR\$5 WITH domain	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/14 16:10
-	39	(BIR\$5 WITH domain) and iap	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/14 16:10
-	27	Robert WITH KORNELUK,	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/05 14:50
-	25	(XIAP M-XIAP HIAP\$3 M-HIAP\$3) SAME BIR\$3	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/05 15:39
-	1	("6511828").PN.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/05 15:40
-	2	("6245523").PN.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/05 15:40
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-	3	"6187557"	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/05 15:49
-	2	("6187557").PN.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/05 18:02

(FILE 'HOME' ENTERED AT 17:38:19 ON 01 MAY 2003)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICINF' ENTERED
AT 17:38:55 ON 01 MAY 2003

L1 0 S INHIBITOR OF APOPTOSIS PROTIEN
L2 1411 S INHIBITOR OF APOPTOSIS PROTEIN
L3 184 S L2 AND BIR?
L4 46 S L3 AND (BIRIII OR BIR-III OR BIR3 OR BIR-3)
L5 21 DUP REM L4 (25 DUPLICATES REMOVED)
L6 21 FOCUS L5 1-

=> d an ti so au ab l6 1 4 6 10 11 21

L6 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2003 ACS
AN 2003:58269 CAPLUS
DN 138:120454
TI Identification of Omi/HtrA2 as a mitochondrial apoptotic serine proteinase
that disrupts **inhibitor of apoptosis protein**
-caspase interaction and its therapeutic use
SO PCT Int. Appl., 83 pp.
CODEN: PIXXD2
IN Alnemri, Emad S.
AB An isolated nucleic acid mol. comprising a polynucleotide having a
sequence encoding a peptide or polypeptide of Omi having at least an
N-terminus amino acid sequence of Ala-Val-Pro-Ser which is capable of
specifically binding to at least a portion of an **Inhibitor of**
Apoptosis protein. The mature serine protease Omi (also
known as HtrA2) was identified as a mitochondrial direct baculoviral
inhibitor of apoptosis protein (IAP) repeat 3
(BIR3) domain-binding protein and a caspase activator. Mature
Omi contains a conserved IAP-binding motif (AVPS) at its N terminus, which
is exposed after processing of its N-terminal mitochondrial targeting
sequence upon import into the mitochondria. Mature Omi is released
together with mature Smac from the mitochondria into the cytosol upon
disruption of the outer mitochondrial membrane during apoptosis. Finally,
mature Omi can induce apoptosis in human cells in a caspase-independent
manner through its protease activity and in a caspase-dependent manner via
its ability to disrupt caspase-IAP interaction. Our results provide clear
evidence for the involvement of a mitochondrial serine protease in the
apoptotic pathway, emphasizing the crit. role of the mitochondria in cell
death. This peptide can be used in a method to modulate apoptosis or to
identify modulators of apoptosis as well as in therapeutic uses.

L6 ANSWER 4 OF 21 MEDLINE
AN 2001038264 MEDLINE
TI NMR structure and mutagenesis of the third **Bir** domain of the
inhibitor of apoptosis protein XIAP.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Oct 27) 275 (43) 33777-81.
Journal code: 2985121R. ISSN: 0021-9258.
AU Sun C; Cai M; Meadows R P; Xu N; Gunasekera A H; Herrmann J; Wu J C; Fesik
S W
AB The **inhibitor of apoptosis proteins** (IAPs)
regulate the caspase family of cysteine proteases, which play an important
role in the execution of programmed cell death. Human X-linked
inhibitor of apoptosis protein (XIAP) is a
potent inhibitor of caspases-3, -7, and -9. Here we show that the
Bir3 domain is the minimal region of XIAP that is needed for
potent caspase-9 inhibition. The three-dimensional structure of the
Bir3 domain of XIAP, determined by NMR spectroscopy, resembles a
classical zinc finger and consists of five alpha-helices, a three-stranded
beta-sheet, and a zinc atom chelated to three cysteines and one histidine.
The structure of the **Bir3** domain is similar to that of the
Bir2 domain of XIAP but differs from the previously determined
structure of the **Bir3** domain of MIHB. Based on site-directed
mutagenesis, we have identified the regions of the **Bir3** domain
of XIAP that are important for inhibiting caspase-9. Despite the
structural similarities of the **Bir2** and **Bir3** domain of
XIAP, a different set of residues were found to be critical for inhibiting
the individual caspases. These results suggest that XIAP inhibits
caspase-3 and caspase-9 in a different manner.

L6 ANSWER 6 OF 21 MEDLINE
AN 1999438002 MEDLINE

TI Cleavage of human inhibitor of apoptosis
protein XIAP results in fragments with distinct specificities for
caspases.
SO EMBO JOURNAL, (1999 Oct 1) 18 (19) 5242-51.
Journal code: 8208664. ISSN: 0261-4189.
AU Deveraux Q L; Leo E; Stennicke H R; Welsh K; Salvesen G S; Reed J C
AB Several human inhibitor of apoptosis (IAP) family proteins function by
directly inhibiting specific caspases in a mechanism that does not require
IAP cleavage. In this study, however, we demonstrate that endogenous XIAP
is cleaved into two fragments during apoptosis induced by the tumor
necrosis factor family member Fas (CD95). The two fragments produced
comprise the baculoviral inhibitory repeat (BIR) 1 and 2 domains
(BIR1-2) and the BIR3 and RING (BIR3-Ring)
domains of XIAP. Overexpression of the BIR1-2 fragment inhibits
Fas-induced apoptosis, albeit at significantly reduced efficiency compared
with full-length XIAP. In contrast, overexpression of the BIR3
-Ring fragment results in a slight enhancement of Fas-directed apoptosis.
Thus, cleavage of XIAP may be one mechanism by which cell death programs
circumvent the anti-apoptotic barrier posed by XIAP. Interestingly,
ectopic expression of the BIR3-Ring fragment resulted in nearly
complete protection from Bax-induced apoptosis. Use of purified
recombinant proteins revealed that BIR3-Ring is a specific
inhibitor of caspase-9 whereas BIR1-2 is specific for caspases 3
and 7. Therefore XIAP possesses two different caspase inhibitory
activities which can be attributed to distinct domains within XIAP. These
data may provide an explanation for why IAPs have evolved with multiple
BIR domains.

L6 ANSWER 10 OF 21 MEDLINE
AN 1998192555 MEDLINE

TI A single BIR domain of XIAP sufficient for inhibiting caspases.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Apr 3) 273 (14) 7787-90.
Journal code: 2985121R. ISSN: 0021-9258.
AU Takahashi R; Deveraux Q; Tamm I; Welsh K; Assa-Munt N; Salvesen G S; Reed
J C
AB The inhibitor of apoptosis proteins (IAPs)
constitute an evolutionarily conserved family of homologous proteins that
suppress apoptosis induced by multiple stimuli. Some IAP family proteins,
including XIAP, cIAP-1, and cIAP-2, can bind and directly inhibit selected
caspases, a group of intracellular cell death proteases. These
caspase-inhibiting IAP family proteins all contain three tandem
BIR domains followed by a RING zinc finger domain. To determine
the structural basis for caspase inhibition by XIAP, we analyzed the
effects of various fragments of this IAP family protein on caspase
activity in vitro and on apoptosis suppression in intact cells. The RING
domain of XIAP failed to inhibit the activity of recombinant caspases-3 or
-7, whereas a fragment of XIAP encompassing the three tandem BIR
domains potentially inhibited these caspases in vitro and blocked Fas
(CD95)-induced apoptosis when expressed in cells. Further dissection of
the XIAP protein demonstrated that only the second of the three
BIR domains (BIR2) was capable of binding and inhibiting
these caspases. The apparent inhibition constants (K_i) for BIR2
-mediated inhibition of caspases-3 and -7 were 2-5 nM, indicating that
this single BIR domain possesses potent anti-caspase activity.
Expression of the BIR2 domain in cells also partially suppressed
Fas-induced apoptosis and blocked cytochrome c-induced processing of
caspase-9 in cytosolic extracts, whereas BIR1 and BIR3
did not. These findings identify BIR2 as the minimal
caspase-inhibitory domain of XIAP and indicate that a single BIR
domain can be sufficient for binding and inhibiting caspases.

L6 ANSWER 11 OF 21 MEDLINE
AN 2002303430 MEDLINE

TI Molecular targeting of inhibitor of apoptosis
proteins based on small molecule mimics of natural binding
partners.
SO BIOCHEMISTRY, (2002 Jun 11) 41 (23) 7344-9.

Journal code: 0370623. ISSN: 0006-2960.

AU Kipp Rachael A; Case Martin A; Wist Aislyn D; Cresson Catherine M; Carrell Maria; Griner Erin; Wiita Arun; Albiniaak Philip A; Chai-Ji-jie; Shi-Yigong; Semmelhack-Martin F; McLendon George L

AB An assay based on a solvent-sensitive fluorogenic dye molecule, badan, is used to test the binding affinity of a library of tetrapeptide molecules for the **BIR3** (baculovirus IAP repeat) domain of XIAP (X-linked inhibitor of apoptosis protein). The fluorophore is attached to a tetrapeptide, Ala-Val-Pro-Cys-NH(2), through a thiol linkage and, upon binding to XIAP, undergoes a solvatochromic shift in fluorescence emission. When a molecule (e.g., a natural protein known to bind to XIAP or a tetrapeptide mimic) displaces the dye, the emission shifts back to the spectrum observed in water. As emission intensity is related to the binding of the tetrapeptide, the intensity can be used to determine the equilibrium constant, K, for the displacement of the dye by the tetrapeptide. The results permit residue-specific analysis of the interaction. Furthermore, we show that hydrophobic effects in the fourth position are general and can effectively increase overall affinity.

L6 ANSWER 21 OF 21 MEDLINE

AN 2002075834 MEDLINE

TI Sequence requirements for Hid binding and apoptosis regulation in the baculovirus inhibitor of apoptosis Op-IAP. Hid binds Op-IAP in a manner similar to Smac binding of XIAP.

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Jan 25) 277 (4) 2454-62.
Journal code: 2985121R. ISSN: 0021-9258.

AU Wright Casey W; Clem Rollie J

AB It has been suggested that the Drosophila Hid protein interacts with the baculovirus Op-IAP protein in a manner similar to that of human Smac binding to XIAP, based largely on amino acid sequence homology. However, there is little direct experimental evidence in support of this hypothesis; indeed, evidence exists from previous studies suggesting that the mode of binding is not similar. We have now precisely mapped the interaction between Hid and Op-IAP, and we show clearly for the first time that the biochemical interactions between the amino terminus of Hid and **BIR2** of Op-IAP are highly similar to those found between the processed amino terminus of Smac and **BIR3** of XIAP. Also similar to Smac, the amino terminus of Hid must be processed to bind Op-IAP. In addition, our data also suggest that a second interaction between Hid and Op-IAP exists that does not involve the amino terminus of Hid, which may explain some of the earlier contradictory results. The evolutionary conservation of this mechanism of binding underscores its importance in apoptotic regulation. Nevertheless, interaction with Hid is not sufficient for Op-IAP to inhibit apoptosis induced by Hid overexpression or by treatment with actinomycin D, indicating that additional sequence elements are required for the anti-apoptotic function of Op-IAP.

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☐ 1: 1G73C. Chain C, Crystal ...[gi:13096729][BLink](#), [Domains](#), [Links](#)

LOCUS 1G73_C 121 aa linear PRI 08-NOV-2000
DEFINITION Chain C, Crystal Structure Of Smac Bound To Xiap-Bir3 Domain.
ACCESSION 1G73_C
VERSION 1G73_C GI:13096729
DBSOURCE pdb: molecule 1G73, chain 67, release Nov 8, 2000;
deposition: Nov 8, 2000;
class: ApoptosisAPOPTOSIS INHIBITOR;
source: Mol_id: 1; Organism_scientific: Homo Sapiens;
Organism_common: Human; Gene: Smac; Expression_system: Escherichia
Coli; Expression_system_common: Bacteria; Expression_system_strain:
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Expression_system_plasmid: Pet15-B; Mol_id: 2; Organism_scientific:
Homo Sapiens; Organism_common: Human; Expression_system:
Escherichia Coli; Expression_system_common: Bacteria;
Expression_system_strain: Bl21 (De3);
Expression_system_vector_type: Plasmid; Expression_system_plasmid:
Pet15-B;
Exp. method: X-Ray Diffraction.

KEYWORDS

SOURCE Homo sapiens (human)

ORGANISM [Homo sapiens](#)Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.

REFERENCE 1 (residues 1 to 121)

AUTHORS Wu,G., Chai,J., Suber,T.L., Wu,J.W., Du,C., Wang,X. and Shi,Y.

TITLE Structural basis of IAP recognition by Smac/DIABLO

JOURNAL Nature 408 (6815), 1008-1012 (2000)

MEDLINE 21020962

PUBMED 11140638

REFERENCE 2 (residues 1 to 121)

AUTHORS Wu,G., Chai,J., Suber,T.L., Wu,J.W. and Shi,Y.

TITLE Direct Submission

JOURNAL Submitted (08-NOV-2000)

COMMENT Revision History:

JAN 10 1 Initial Entry.

FEATURES

Location/Qualifiers

source 1..121

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[SecStr](#) 52..55

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[SecStr](#) 60..65

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[SecStr](#) 66..71

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[SecStr](#) 99..107

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121 k

//

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May 1 2003 16:27:42



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☐ 1: AAC50373. X-linked inhibito...[gi:1184320]

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LOCUS AAC50373 497 aa linear PRI 11-FEB-1996
 DEFINITION X-linked inhibitor of apoptosis protein.
 ACCESSION AAC50373
 VERSION AAC50373.1 GI:1184320
 DBSOURCE locus HSU45880 accession [U45880.1](#)
 KEYWORDS .
 SOURCE Homo sapiens (human)

ORGANISM [Homo sapiens](#)
 Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
 Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.

REFERENCE 1 (residues 1 to 497)
 AUTHORS Liston,P., Roy,N., Tamai,K., Lefebvre,C., Baird,S.,
 Cherton-Horvat,G., Farahani,R., McLean,M., Ikeda,J., MacKenzie,A.
 and Korneluk,R.G.

TITLE Suppression of apoptosis in mammalian cells by NAIP and a related
 family of IAP genes
 JOURNAL Nature 379 (6563), 349-353 (1996)
 MEDLINE [96149249](#)
 PUBMED [8552191](#)

REFERENCE 2 (residues 1 to 497)
 AUTHORS Baird,S.D.
 TITLE Direct Submission
 JOURNAL Submitted (16-JAN-1996) Stephen D. Baird, Children's Hospital of
 Eastern Ontario, Genetics, 401 Smyth Rd., Ottawa, Ontario, K1H 8L1,
 Canada

COMMENT Method: conceptual translation.

FEATURES
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 181 prelasagly ytigdgqvc fccgglknw epcdrawseh rrhfpncffv lgrnlnirse
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